FUNDING: Neuronetics provided a grant in kind for the use of equipment.

FINANCIAL DISCLOSURES: Dr. Croarkin has received research support from the Stanley Medical Research Institute and the National Alliance for Schizophrenia and Depression (NARSAD). Dr. Wall has received equipment support from Neuronetics. Ms. King has no conflicts of interest relevant to the content of this article. Dr. Kozel has received financial support from the National Institute of Mental Health, the National Institute of Health, National Center for Research Resources, Neuronetics (grant-in-kind support for supplies and use of equipment), Defense Academy for Credibility Assessment, Cephos Corp., Stanley Medical Research Institute, Cyberonics, and Glaxo Smith Kline; holds patents as an inventor through the Medical University of South Carolina on fMRI Detection of Deception and patents pending for Guided rTMS Inhibition of Deception and optimizing VNS dose with rTMS; and was a 2004 Monthly Case Discussion Group Leader x1 sponsored by Astra Zeneca and an unpaid scientific consultant to Cephos Corp. Dr. Daskalakis received external funding through Neuronetics and Brainsway Inc, Aspect Medical, and a travel allowance through Pfizer and Merck. Dr. Daskalakis also has received speaker funding through Sepracor Inc. and served on the advisory board for Hoffmann-La Roche Limited.

ADDRESS CORRESPONDENCE TO: Paul E. Croarkin, DO, MSCS, Department of Psychiatry and Psychology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Phone: (507) 284-1538; Email: croarkin.paul@mayo.edu

KEY WORDS: Pain, TMS, rTMS, neurophysiology, transmagnetic stimulation

CASE SERIES

Pain During Transcranial Magnetic Stimulation in Youth

by PAUL E. CROARKIN, DO, MSCS; CHRISTOPHER A. WALL, MD; JESSICA D. KING, BA; F. ANDREW KOZEL, MD, MSCR; and ZAFIRIS J. DASKALAKIS, MD, PhD, FRCPC

Drs. Croarkin and Wall are with the Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota (Dr. Croarkin was with the Department of Psychiatry, Division of Child and Adolescent Psychiatry, UT Southwestern Medical Center, Dallas, Texas, at the time of this study); Ms. King is with the Department of Psychiatry, Division of Child and Adolescent Psychiatry, UT Southwestern Medical Center, Dallas, Texas; Dr. Kozel is with the Department of Psychiatry, Division of Child and Adolescent Psychiatry, UT Southwestern Medical Center, Dallas, Texas, and the Department of Psychiatry and Neuroscience, USF Health-College of Medicine, University of South Florida, Tampa, Florida; and Dr. Daskalakis is with the Brain Stimulation Research and Treatment Program, Centre for Addiction and Mental Health,Toronto, Ontario, Canada.

Innov Clin Neurosci. 2011;8(12):18–23

ABSTRACT

Pain or discomfort at the site of stimulation is a common side effect of transcranial magnetic stimulation. Relevant physiology and predisposing factors have not been adequately described. Literature regarding work with minors is even more limited. The authors present two cases from a child and adolescent neurophysiology transcranial magnetic stimulation protocol and one case from a therapeutic study of repetitive transcranial magnetic stimulation in adolescents with treatment-resistant major depressive disorder. Relevant literature is reviewed. Potential subjects, parents, and study teams should be well aware of this potential side effect in child and adolescent populations. Subjects with anxiety disorders may be prone to pain during these procedures. Further work could assist in identifying predisposed individuals, refining the informed consent process, and implementing procedures to minimize discomfort.

INTRODUCTION

Transcranial magnetic stimulation is a noninvasive procedure in which the brain is stimulated by brief magnetic pulses. Each pulse is approximately 50 microseconds and is created by rapid changes in electrical current that travels through a coil. These magnetic pulses penetrate the scalp relatively unimpeded and induce electric fields in the cortical tissue. Single and paired-pulse TMS paradigms are used principally for the noninvasive exploration of the cortex. These techniques have contributed to the understanding of the neurophysiology of psychiatric disorders.[1,2] Repetitive transcranial magnetic stimulation (rTMS) consists of trains of magnetic pulses, typically applied to the prefrontal cortex for therapeutic purposes. This procedure has been used most extensively for the treatment of major depression in adults and was cleared by the United States Food and Drug Administration (FDA) in 2008 for a subset of patients with major depressive disorder (MDD).[3,4] Multiple meta-analyses have also demonstrated its efficacy in the treatment of adults with depression.[5–7] The procedure is generally well tolerated, which makes rTMS a feasible treatment option for individuals with depression who do not respond adequately to medication or therapy.[8,9]

TMS IN CHILDREN AND ADOLESCENTS

Previously, single- and paired-pulse TMS techniques have been employed in the study of children and adolescents.[10–14] Worldwide, published data from over 80 studies indicates that at least 800 healthy controls and over 300 neurologically abnormal children have been exposed to single and paired-pulse TMS paradigms.[15–17] These investigations can be broadly categorized into the examinations of the neurophysiology of normal development, cortical motor map reorganization after damage to the central nervous system, and the neurophysiology of abnormalities (i.e., psychiatric, medical, or neurological). No serious adverse events have been documented, and experts have argued that single- and paired-pulse TMS are minimal-risk procedures.[10,15]

Conversely, comparably few studies have examined the application of rTMS in child and adolescent populations.[17–21] Therapeutic studies of rTMS primarily involve adolescent case studies or small open-label trials of subjects with MDD.[17,21,22] In general, these rTMS procedures have been well tolerated.[16,21] Recent reviews on this subject underscore the need for further investigation of rTMS as a therapeutic treatment for this population.[17,21]

PAIN AND INTOLERABILITY OF TMS

Most adult participants relate that single- and paired-pulse TMS are painless.[23] On the other hand, as many as 40 percent of subjects relate pain or discomfort during rTMS.[24,25] Commonly, this includes local pain, headaches, or nonspecific discomfort.[26] Pain related to cortical TMS is most likely due to stimulation of the facial and trigeminal nerves, contractions of facial muscles, or the activation of nociceptors in the scalp and bone beneath the coil.[27] Fortunately, in the majority of cases, these effects are transient. However, this does increase subject burden and contributes to drop out in clinical studies.[23] Moreover, pain from an active rTMS condition in a sham-controlled, blinded study is problematic from a methodological perspective as it likely contributes to unblinding of both subjects and investigators.[28–30]

Borckardt et al[31] previously examined four strategies to manage discomfort in healthy adults during the course of left prefrontal rTMS (10 Hz for 5 seconds on and 30 seconds off, at 100% and 120% of resting motor threshold) in a descriptive study. This included a topical eutectic mixture of local anesthetic (EMLA) cream (two subjects underwent rTMS with this strategy), subcutaneous injections of 1% lidocaine (two subjects underwent rTMS with this strategy), subcutaneous injections of 1% lidocaine and epinephrine (three subjects underwent rTMS with this strategy), and placement of three-inch by three-inch foam sheets under the rTMS coil and over the scalp (three subjects underwent this strategy). Pre- and post-rTMS pain and unpleasantness ratings were collected with a visual analog scale (VAS). Of note, the EMLA cream did not seem to impact pain intensity during either rTMS session. With the lidocaine injection, subjects related a 56-percent reduction in pain and 62-percent reduction in unpleasantness during the 100-percent motor threshold sessions. During the 120-percent motor threshold rTMS sessions, there was a 27-percent reduction in pain and a 51-percent reduction in unpleasantness. The injections were well tolerated and rated as more tolerable than baseline rTMS. The lidocaine and epinephrine injections decreased pain intensity by 74 percent and unpleasantness by 67 percent with 100-percent motor threshold sessions. Pain intensity decreased by 55 percent and unpleasantness decreased by 52 percent with 120-percent motor threshold sessions. The analgesic effect of lidocaine injections were maintained, to a lesser degree, 30 minutes later. Finally, the foam padding conferred a 7.2-percent reduction in pain intensity and 6.1-percent reduction in unpleasantness with 100-percent motor threshold rTMS; and 5.3-percent reduction in pain intensity and 8.4-percent reduction in unpleasantness with rTMS at 120-percent motor threshold. The authors suggested that these results might provide insight into the mechanisms of pain in prefrontal rTMS. Namely, this suggests that nociceptors in the periosteum or meninges may be implicated in rTMS-induced pain.[31]

More recently, Trevino et al[32] examined the use of topical lidocaine HCL 2% applied 20 minutes prior to rTMS treatments in 10 subjects who had endorsed pain during the procedure. Participants were enrolled in a clinical trial of high frequency rTMS. Each session was 3,000 pulses, four seconds on, 26 seconds off, of 10 Hz rTMS delivered to the left dorsolateral prefrontal cortex at 120-percent motor threshold.[33] Based on randomization, response, and adherence, these subjects were exposed to a range of 2 to sixty-three rTMS sessions. Results of this case series were mixed in that 50% of participants reported no benefit in pain reduction with the use of topical lidocaine, while the other 50% related a perceptible decrease in pain of the sessions. Of the five subjects that had no benefit, only one was able to adhere to the full course of the rTMS protocol. The five subjects that had benefitted from the topical lidocaine were able to continue rTMS sessions, but one ultimately dropped out of the study early due to scheduling. Four of these participants eventually acclimated to rTMS sessions, and subsequently the topical lidocaine was discontinued. The authors suggested that some patients might benefit from topical lidocaine as rTMS treatment courses are initiated.[32]

Investigators have suggested that the risks and discomforts arising from the use of single- and paired-pulse TMS in children are commensurable to common medical tests, and TMS has been deemed to have an excellent safety profile in this population.[15,16] Of the adolescents undergoing rTMS as a therapeutic treatment, limited adverse effects were reported and were generally limited to headaches.[21,22] In a study by Garvey et al.,[40] children's subjective thoughts on TMS were gathered. Among eight common childhood experiences, TMS was ranked fourth—better than a long car ride, but not as good as watching TV. Generally, TMS seemed to be well received by the children in the study. Two subjects (5%) discontinued the TMS procedure due to intolerability. Six of the 40 participants said they would not do TMS again.[34] There does appear to be a subset of child and adolescent subjects that finds TMS procedures unsettling or intolerable. There are many factors that could contribute to feelings of unease with TMS, including variability in individual pain level and anxiety. At the present time, very little is known about patients with intolerable pain during TMS. The following case series will review three instances of pain and intolerability during child and adolescent TMS procedures with the goals of informing researchers and potential subjects. This may also serve as a basis for further work in this important aspect of TMS research.

CASE SERIES

Case 1: pain with single-pulse TMS. After obtaining assent and informed consent, a 10-year-old girl enrolled in the single- and paired-pulse TMS study as a healthy control. Her parents related a life-long pattern of anxiety in school settings and transient difficulties with separation during preschool. These symptoms never caused significant impairment and did not meet the threshold for diagnosis of separation anxiety disorder, generalized anxiety disorder, or any other anxiety disorder based on a Schedule for Affective Disorders and Schizophrenia for School-Age Children--Present and Lifetime Version (K-SADS-PL)[35] interview by a child and adolescent psychiatrist. Otherwise, she had no prior psychiatric history. Her family history was significant for anxiety. Her maternal grandmother and maternal aunt had both been treated with benzodiazepines and other unspecified psychotropics. During the evaluation, the subject's Childhood Depression Rating Scale Revised (CDRS-R)[36] score was 18. This subject had a developmentally appropriate understanding of the TMS procedures, had asked appropriate questions, and had indicated to her mother she was eager to be a subject in the present study. She was prepped in the usual fashion with disposable electromyography electrodes affixed to the abductor pollicis brevis (APB) muscle, a swim cap, and ear plugs. Motor threshold testing commenced with a Magstim 200 (Carmarthenshire, Wales, United Kingdom) utilizing the estimation of limits method. Stimulation intensity was increased gradually. At 56-percent intensity, she indicated intolerable scalp pain and wanted to withdraw from the study. TMS testing was discontinued immediately and she was observed in the lab over 30 minutes. She denied ongoing pain or anxiety and went home with her parents. A week later, she denied any ongoing pain, anxiety, or symptoms.

Case 2: pain with single-pulse TMS. After obtaining assent and informed consent, a 10-year-old girl enrolled in the single and paired-pulse TMS study as a depressed subject. Based on a KSADS-PL interview with a child and adolescent psychiatrist she met criteria for MDD, single episode, moderate. Separation anxiety disorder was a secondary diagnosis as she had fear of harm befalling attachment figures, fear of events leading to separation from attachment figures, and difficulty sleeping away from home or alone. She also endorsed multiple somatic symptoms and obsessional concerns about her health. In addition to MDD symptoms, this anxiety had been significantly impairing as it had impacted her school performance and ability to make friends. On exam, her CDRS-R score was 47. She had no other psychiatric history and no prior treatment. There was no significant medical history. There was no family psychiatric history. This subject had a developmentally appropriate understanding of the TMS procedures and had asked appropriate questions. Of note, the initial informed consent conversation took longer than usual, but the patient and her parents related that they were comfortable with the idea of her participation. She was prepped in the usual fashion with disposable electromyography electrodes affixed to the abductor pollicis brevis (APB) muscle, a swim cap, and ear plugs. Motor threshold testing was commenced with a Magstim 200 utilizing the estimation of limits method. Stimulation intensity was increased gradually. At 40-percent intensity, she began crying and indicated intolerable scalp pain. She asked to withdraw from the study. TMS testing was discontinued immediately and she was observed in the lab over 30 minutes. She denied ongoing pain or anxiety and went home with her parents. A week later, she denied any ongoing pain, anxiety, or symptoms. At follow up, she ultimately reached remission of depressive symptoms after treatment with 20mg of fluoxetine daily. Over six months, she denied any ongoing pain or anxiety related to her brief exposure to single-pulse TMS.

Case 3: pain with rTMS. After obtaining assent and informed consent, a 17-year-old girl with chronic, severe MDD enrolled in an open-label, therapeutic trial of rTMS with the Neuronetics Model 2100 System investigational device (Malvern, Pennsylvania). On evaluation with a KSADS-PL by a child and adolescent psychiatrist she met criteria for MDD, dysthymic disorder, and separation anxiety disorder. Her CDRS-R was 62. This patient had failed multiple previous medication trials due to lack of efficacy or intolerable side effects. This included escitalopram 10mg daily for six weeks, sertraline 75mg daily for four weeks, paroxetine CR 25mg daily by mouth for four weeks, and bupropion XL 300mg for 20 weeks. She had two previous unsuccessful courses of psychotherapy. At the commencement of rTMS sessions, she had been on fluoxetine 40mg daily for six weeks as per the study protocol. This subject tolerated a motor threshold procedure with no pain or difficulties. Her motor threshold was 41 percent of maximum machine output. Subsequently, rTMS was initiated. She related discomfort after six trains. The intensity was described as 7 out of 10, with 10 being the most intense, and characterized as a "headache-it is sort of like a migraine behind my eyes." The rTMS session was discontinued. The subject and her parents were offered the option of discontinuing or another session after pretreatment with ibuprofen and topical 2% lidocaine. She elected to try again and, on the following morning, was pretreated with 600mg of ibuprofen and topical 2% lidocaine. After four trains of rTMS, she again related that she did not want to continue the session. The rTMS session was discontinued, she exited the study, and was referred for ongoing medication management. A year later, she denied any ongoing pain or anxiety related to the rTMS session but had no interest in pursuing this option in the future despite ongoing functional impairment and suboptimal results from ongoing medication management and psychotherapy.

DISCUSSION

The first two subjects in this case series were the only subjects of 52 (3.8%) child and adolescent subjects ages 7 to 18 unable to tolerate single-pulse TMS due to pain. The final subject described was one of eight adolescents (12.5%) ages 13 to 18 enrolled in an open-label trial of rTMS for treatment-resistant depression who dropped out due to pain. This is encouraging as the majority of children and adolescents in these two protocols did tolerate single-pulse, paired-pulse, and repetitive TMS procedures. Importantly, the three participants described who were not able to tolerate TMS did not have any lasting sequela from the procedure. It is also notable that these three subjects either had mild comorbid anxiety or a family history of anxiety.

In adult neurophysiology literature, depressed subjects and healthy controls appear to tolerate single and paired-pulse TMS procedures without difficulties or this is simply is not commented on.[37,38] Similar research involving children and adolescents typically describes this in greater detail. In a TMS study by Garvey et al,[34] two (5%) child subjects of 40 discontinued because they were uncomfortable.[34] In a follow-up safety study with 34 children, Gilbert et al[15] related that 12 percent related scalp discomfort, six percent related a headache, six percent related neck pain, and six percent related arm pain.[15]

In the largest rTMS trial for MDD to date, O'Reardon et al[33] reported that of patients receiving active, high frequency rTMS (n=165), 18 (10.9%) subjects reported site discomfort, 59 (35.8%) reported application site pain, and 11 (6.7%) reported facial pain. In another adult rTMS trial for MDD, George et al[39] related that of the subjects receiving active rTMS (n=92), 29 (32%) reported a headache and 17 (18%) reported discomfort at the stimulation site. Previously, Fitzgerald et al[40] described a trial comparing high-frequency rTMS, low-frequency rTMS, and sham stimulation in subjects with treatment-resistant depression (N=60, with 20 subjects in each group). These authors conveyed that seven (11%) subjects reported site discomfort during rTMS and six (10%) reported a headache. Although, there was no difference between rTMS treatments, the investigators commented that, in general, subjects receiving high frequency rTMS appeared to relate more discomfort during the procedure. Moreover, one of these adult subjects did withdraw after one session of high frequency rTMS.[40]

As TMS research and clinical practice evolves, pain and tolerability associated with these procedures must be fully characterized and studied in detail. First and foremost, this could decrease subject burden in research protocols and mitigate this common side effect in clinical practice. Potential subjects and enrolled subjects must be well aware of this adverse effect during the informed consent process. Further understanding could inform researchers and subjects as to predisposing characteristics in this regard. Finally, this could also inform the methodology of TMS studies and clinical care to reduce this potential burden. For example, initial titration schedules or application of topical lidocaine might be beneficial early in the course of rTMS. Induced pain with active TMS must also be considered in blinded, sham-controlled studies. As the body of TMS research evolves, these considerations are even more important in research involving vulnerable populations such as children and adolescents.

REFERENCES

1. Lisanby SH, Luber B, Perera T, Sackeim HA. Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology. *Int J Neuropsychopharmacol.* 2000;3(3):259–273.
2. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? *Nat Rev Neurosci.* 2007;8(7):559–567.
3. Medical devices, neurological devices, classification of repetitive transcranial magnetic stimulation system. Final rule. *Fed Regist.* 2011 26;76(143):44489-44491.
4. Hadley D, Anderson BS, Borckardt JJ, et al. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for treatment-resistant depression in a clinical setting. *J ECT.* 2011;27(1):18–25.
5. Schonfeldt-Lecuona C, Cardenas-Morales L, Freudenmann RW, et al. Transcranial magnetic stimulation in depression--lessons from the multicentre trials. *Restor Neurol Neurosci.* 2010;28(4):569–576.
6. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract.* 2002;8(5):270–275.
7. Pridmore S. Therapeutic use of rTMS (correspondence). *Nat Rev Neurosci.* 2007;12: doi10.1038/nrn2169-c1.
8. Daskalakis ZJ. Repetitive transcranial magnetic stimulation for the treatment of depression: To stimulate or not to stimulate? *J Psychiatry Neurosci.* 2005;30(2):81–82.
9. Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. *Can J Psychiatry.* 2008;53(9):555–566.
10. Garvey MA, Gilbert DL. Transcranial magnetic stimulation in children. *Eur J Paediatr Neurol.* 2004;8(1):7–19.
11. Garvey MA, Barker CA, Bartko JJ, et al. The ipsilateral silent period in boys with attention-deficit/hyperactivity disorder. *Clin Neurophysiol.* 2005;116(8):1889–1896.
12. Gilbert DL, Sallee FR, Zhang J, Lipps TD, Wassermann EM. Transcranial magnetic stimulation-evoked cortical inhibition: a consistent marker of attention-deficit/hyperactivity disorder scores in tourette syndrome. *Biol Psychiatry.* 2005;57(12):1597–600.
13. Frye RE, Rotenberg A, Ousley M, Pascual-Leone A. Transcranial magnetic stimulation in child neurology: current and future directions. *J Child Neurol.* 2008;23(1):79–96.
14. Gilbert DL, Isaacs KM, Augusta M, et al. Motor cortex inhibition: a marker of ADHD behavior and motor development in children. *Neurology.* 2011;76(7):615–621.
15. Gilbert DL, Garvey MA, Bansal AS, et al. Should transcranial magnetic stimulation research in children be considered minimal risk? *Clin Neurophysiol.* 2004;115(8):1730–1739.
16. Quintana H. Transcranial magnetic stimulation in persons younger than the age of 18. *J ECT.* 2005;21(2):88–95.
17. Croarkin PE, Wall CA, McClintock SM, et al. The emerging role for repetitive transcranial magnetic stimulation in optimizing the treatment of adolescent depression. *J ECT.* 2010;26(4):323–329.
18. Walter G, Martin J, Kirkby K, Pridmore S. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Aust N Z J Psychiatry.* 2001;35(1):58–61.
19. Loo C, McFarquhar T, Walter G. Transcranial magnetic stimulation in adolescent depression. *Australas Psychiatry.* 2006;14(1):81–85.
20. Bloch Y, Grisaru N, Harel EV, et al. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. *J ECT.* 2008;24(2):156–159.
21. Wall CA, Croarkin PE, Sim LA, et al. Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: a prospective, open pilot study. *J Clin Psychiatry.* 2011;72(9):1263–1269.
22. Walter G, Tormos JM, Israel JA, Pascual-Leone A. Transcranial magnetic stimulation in young persons: a review of known cases. *J Child Adolesc Psychopharmacol.* 2001;11(1):69–75.
23. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009;120(12):2008–2039.
24. Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol.* 2008;11(1):131–147.
25. Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clin Neurophysiol.* 2006;117(2):455–471.
26. Rossi S, De Capua A, Tavanti M, et al. Dysfunctions of cortical excitability in drug-naive posttraumatic stress disorder patients. *Biol Psychiatry.* 2009;66(1):54–61.
27. Borckardt JJ, Smith AR, Reeves

ST, et al. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. *Pain Res Manag.* 2007;12(4):287–290.
28. Lisanby SH, Gutman D, Luber B, et al. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry.* 2001;49(5):460–463.
29. Sommer J, Jansen A, Drager B, et al. Transcranial magnetic stimulation--a sandwich coil design for a better sham. *Clin Neurophysiol.* 2006;117(2):440–446.
30. Rossi S, Ferro M, Cincotta M, et al. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). *Clin Neurophysiol.* 2007;118(3):709–716.
31. Borckardt JJ, Smith AR, Hutcheson K, et al. Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. *J ECT.* 2006;22(4):259–264.
32. Trevino K, McClintock SM, Husain MM. The use of topical lidocaine to reduce pain during repetitive transcranial magnetic stimulation for the treatment of depression. *J ECT.* 2011;27(1):44–47.
33. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry.* 2007;62(11):1208–1216.
34. Garvey MA, Kaczynski KJ, Becker DA, Bartko JJ. Subjective reactions of children to single-pulse transcranial magnetic stimulation. *J Child Neurol.* 2001;16(12):891–894.
35. Kaufman J, Birmaher B, Brent DA, et al. K-Sads-Pl. *J Am Acad Child Adolesc Psychiatry.* 2000;39(10):1208.
36. Poznanski EO, Grossman JA, Buchsbaum Y, et al. Preliminary studies of the reliability and validity of the children's depression rating scale. *J Am Acad Child Psychiatry.* 1984;23(2):191–197.
37. Bajbouj M, Lisanby SH, Lang UE, et al. Evidence for impaired cortical inhibition in patients with unipolar major depression. *Biol Psychiatry.* 2006;59(5):395–400.
38. Levinson AJ, Fitzgerald PB, Favalli G, et al. Evidence of cortical inhibitory deficits in major depressive disorder. *Biol Psychiatry.* 2010;67(5):458–464.
39. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry.* 2010;67(5):507–516.
40. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry.* 2003;60(10):1002–1008. ■